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EXAMINER

SAJJADI, FEREDYDOUN GHOTB

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/463,890	Applicant(s) KOSZINOWSKI ET AL.	
	Examiner FEREYDOUN G. SAJJADI	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36,37 and 40-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36,37 and 40-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' amendment dated October 14, 2008, to the non-final action dated June 19, 2008, has been entered. Claim 36 has been amended. No claims were cancelled or newly added. Accordingly, claims 36, 37 and 40-70 remain pending in the application and are under current examination.

Response & Withdrawn Claim Rejections - 35 USC § 102

Claims 36, 37, 40, 42, 48, 51, 54, 57, 58, and 64-66 were rejected under 35 U.S.C. 102(b) as being anticipated by Messerle et al. (1996) *J. Mol. Med.* 74:B8 (previously made of record). Applicants have amended base claim 36 to recite that the host cell does not contain any HSV genes or proteins, thus obviating the ground for rejection. Accordingly, the previous rejection is hereby withdrawn.

Response & Withdrawn Claim Rejections - 35 USC § 103

Claim 41 was rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*); claim 43 was rejected under 35 U.S.C. 103(a) as being unpatentable over Tomkinson et al. (1993) *J. Virol.* 67:7298-7306 in view of Messerle (*supra*); claim 44 was rejected under 35 U.S.C. 103(a) as being unpatentable over Tomkinson et al. (*supra*) in view of Messerle et al. (*supra*), as applied to claim 43 above, and further in view of Ehtisham et al. (1993) *J. Virol.* 67:5247-5252; claims 45-47, 49, 50, 52, 53, 55 and 56 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*), as applied to claim 36 above, in view of Gage et al. (1992) *J. Virol.* 66:5509-5515; claim 59 was rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*) in view of Roizman et al. (1985) *Science* 229:1208-1214; claims 60-63 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*) in view of Roizman et al. (*supra*) and further in view of Chen et al. (1987) *Mol. Cell. Biol.* 7:2745-2752; and claims 67-70 were rejected under 35 U.S.C. 103(a) as being unpatentable

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over Messerle et al. (*supra*) in view of Luckow et al. (1993) *J. Virol.* 67:4566-4579, in the previous office action dated June 19, 2008.

Applicants have amended base claim 36 to recite that the host cell does not contain any HSV genes or proteins, thus obviating the grounds for rejection. The reference of Messerle et al. does not teach a BAC containing an infectious HSV genomic sequence larger than 100 kb capable of autonomous replication without a helper cell. Accordingly, the previous rejections are hereby withdrawn.

The claims are however subject to new rejections over the prior art as set forth below.

New Claim Rejections - 35 USC § 103

Claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (of record), in view of Chartier et al. (*J. Virol.* 70:4805-4810; 1996).

Messerle et al describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions (i.e., due to complementation between the two vectors upon co-transformation in eukaryotic host cells). The ability of the BAC vectors to produce infectious virus evidences that each of the vectors comprise “parts of the genome of a virus that are indispensable for replication and packaging”. Furthermore, Messerle et al. describe production of the BAC vectors by cotransfection in *E. coli* cells. Messerle et al. state that the purpose of constructing the BAC vectors was to facilitate the exchange of nonessential viral genes by any gene of choice without the need for further selection. Moreover, Messerle et al. notes that human CMV as well as mouse CMV comprises a region that is probably not essential for replication *in vitro* and clearly views human CMV as a potential vector.

While Messerle et al. describe their BAC vectors as comprising two fragments, the generation of large full-length viral vectors by homologous recombination in *E. coli* was known in the prior art.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in

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permissive cells (Title and Abstract). Such is depicted in Figure 1, p. 4806, showing *in vivo* homologous recombination between sequences that include the ITRs (i.e. identical to each other) and the generation of virus plaques after transfection by calcium phosphate (first column, p. 4807) in human (293) or mammalian cells to produce pure Ad5 virus (first column, p. 4810). Thus providing the motivation to apply the methodology to generate full-length infectious virus.

The teachings of Messerle et al. and Chartier et al. are both directed to the reconstitution and generation of infectious viral vectors. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to use homologous recombination mediated by *E. coli*, to generate infectious HSV in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous HSV BAC vector, because such would obviate the need to manipulate two separate BAC fragments.

Claims 43 and 44 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Ehtisham et al. (1993) J. Virol. 67:5247-5252.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Messerle et al. and Chartier et al. do not describe their viruses as including gamma herpes virus MHV68, such was known in the prior art. The method of Chartier et al. is further applicable to any large virus genome.

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Ehtisham et al. describe murine herpes virus 68 (MHV-68) as a naturally occurring murine herpes virus closely related to the EBV of primates. (See especially the first paragraph after the abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to apply homologous recombination mediated by *E. coli*, to generate infectious MHV-68 in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous MHV-68 BAC vector, because such would obviate the need to manipulate two or more separate BAC fragments.

Claims 45-50 and 52-56 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Gage et al. (1992) J. Virol. 66:5509-5515.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Chartier et al. describe recombination between the ITRs of the virus, neither Messerle et al. nor Chartier et al. describe recombination involving loxP sites. However, such was known in the prior art.

Gage et al. describe a method of inserting plasmid DNA into a herpes virus genome by Cre-lox recombination wherein the bacterial sequences are flanked by loxP sites (see especially the paragraph bridging pages 5509-5510, Figure 1 and the caption thereto) and further state the method has many advantages over methods of inserting bacterial DNA by homologous recombination using marker transfer (see especially the first full paragraph on page 5514).

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Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to modify the method of producing a BAC comprising an infectious herpes virus genomic sequence according to the method of Gage et al. such that the product BAC comprises bacterial nucleic acid sequences flanked by loxP sites, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the method of Gage et al. in view of the many advantages of the method described in the teachings of Gage et al. because Gage et al. demonstrates the efficacy of the Cre-lox system for inserting bacterial DNA into the herpes virus genome.

Claims 60-62 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view Chen et al. (1987) Mol. Cell. Biol. 7:2745-2752.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Chartier et al. describe calcium phosphate mediated transfection of 293 cells, neither Messerle et al. nor Chartier et al. describe transfection of NIH3T3 fibroblasts. However, such was known in the prior art.

Chen et al. describe a method of efficiently transformation eukaryotic cells, including NIH3T3 cells, by a method involving calcium phosphate coprecipitation. (See especially the Abstract and Table 1)

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to transfect NIH3T3 cells, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the NIH3T3

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cells, because Chen et al. state that the method provides efficient transformation for introducing DNA.

Claims 67-70 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Luckow et al. (1993) J. Virol. 67:4566-4579 (of record).

The claims are directed to a method of mutagenizing the infectious herpes virus genomic sequence of claim 36 comprising introducing the BAC of claim 36 into a bacterial host and exposing the BAC to mutagenizing DAN molecules, wherein there is a transposon in the mutagenizing DNA molecules.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions. Messerle et al. state that the BACs will facilitate the exchange of nonessential viral genes by any gene of choice.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While neither Messerle et al. nor Chartier et al. describe mutagenizing the infectious HSV genomic sequence with a transposon, such was known in the prior art.

Luckow et al. describe the construction and use of BAC vectors that comprise an infectious viral genome sequence operatively fused to a mini-F replicon that allows autonomous replication and stable segregation of plasmids at low copy number in *E. coli*. The BAC vectors further comprise a selectable kanamycin resistance marker and attTn7 sites that allow transposon-mediated insertion of heterologous nucleic acid sequences into the vector (e.g. Abstract; page 4567, columns 1-2, bridging paragraph; Figure 1). Luckow et al further describe transposon-mediated mutagenesis at the attTn7 sites of different BAC vectors in *E. coli* to generate new vectors comprising a heterologous sequence encoding a desired polypeptide. (See

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especially the section entitled "Transposition of mini-Tn7 elements to target bacmids" bridging the left and right columns on page 4573).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to combine their respective teachings and use the transposon mediated DNA exchange described by Luckow et al. for the purpose of exchanging nonessential viral genes with gene of choice in the BACs of Messerle et al., with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to combine the teachings of the prior art because Messerle et al. teaches that intended use of the BAC vectors described therein is to facilitate the exchange of nonessential CMV viral genes by any gene of choice and Luckow et al. teaches that the method of the transposon mediated DNA exchange described thereby provides many advantages over other methods of engineering viral genomic DNA comprised in BACs that were known in the prior art. (See especially the first full paragraph on page 4577.)

Conclusion

Claims 36, 37 and 40-70 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Fereydoun G Sajjadi/
Examiner, Art Unit 1633